

WHAT IS CLAIMED IS:

1. A non-naturally occurring peptide ligand which competes for binding HER2 in an in vitro assay with a peptide ligand having the formula:

Xaa₍₁₋₁₄₎-Cys-Xaa₁₆-Gly-Pro-Gly-Cys-Xaa₍₂₁₋₂₇₎ (SEQ ID NO:90)

wherein X₍₁₋₁₄₎ is absent or between one and fourteen amino acids; Xaa₁₆ is an amino acid selected from the group consisting of Met, Thr, Cys and Ile and Xaa₍₂₁₋₂₇₎ is absent or between one and 7 amino acids.

2. The peptide ligand of claim 1 having the following formula:

Xaa₍₁₋₇₎-Cys-Xaa₉-Gly-Pro-Gly-Cys-Xaa₍₁₄₋₂₀₎ (SEQ ID NO:92)

wherein X₍₁₋₇₎ is absent or between one and seven amino acids; and Xaa₉ is an amino acid selected from the group consisting of Met, Ile, Thr or Cys and Xaa₍₁₄₋₂₀₎ is absent or between one and seven amino acids.

3. The peptide ligand of claim 2 having the following formula:

Xaa₍₁₋₇₎-Cys-Ile-Gly-Pro-Gly-Cys-Xaa₍₁₄₋₂₀₎ (SEQ ID NO:161).

4. A peptide ligand having the formula A-A wherein A is the peptide ligand of claim 3 and "-" is an optional linker domain.

5. The peptide ligand of claim 3 having the following formula:

Xaa₍₁₋₅₎-Trp-Gly-Cys-Ile-Gly-Pro-Gly-Cys-Xaa₍₁₄₋₂₀₎ (SEQ ID NO:93)

wherein Xaa₍₁₋₅₎ is absent or between one and five amino acids.

6. The peptide ligand of claim 5 having the following formula:

~~Xaa₍₁₋₃₎-Glu-Xaa₅-Trp-Gly-Cys-Ile-Gly-Pro-Gly-Cys-Xaa₁₄-Xaa₁₅-
Leu-Xaa₍₁₇₋₂₀₎ (SEQ ID NO:87)~~

wherein Xaa₍₁₋₃₎ is absent or between one and three amino acids,
Xaa₅ is an amino acid,
Xaa₅ is an amino acid,
Xaa₁₄ is an amino acid,
Xaa₁₉ is an amino acid and
-Xaa₍₁₇₋₂₀₎ is absent or between one and four amino acids.

7. The peptide ligand of claim 6 wherein X₍₁₋₃₎- is absent or selected from the group consisting of

Gln-Arg-Asn-
Leu-Ser-Pro-
Glu-Asn-Trp-
Ala-Ser-His-
Lys-Leu-Asn-
Thr-Gln-Ala-
Ala-Pro-Arg-
Gln-Val-Tyr-
Arg-Thr-Glu-
Phe-Ala-Gly-
Thr-Ala-Arg-
Arg-Pro-His-
Asn-Val-Cys-
Cys-Ile-Asp-
Tyr-Glu-Trp-
Arg-Trp-Asp-
His-Trp-Met-
Asn-Trp-Pro-
Phe-Asn-Trp-

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Ala, Thr, Met, Val, Arg, Glu, Asp, Ser, Gln, Pro, Gly, Phe and
Lys,

Glu, Lys, Arg, ~~Asp~~, Ser, Ala, Asn, Gly, Pro and Gln,

Met, Phe, Ala, Met, Cys, Gln, Glu, Ala, Trp, Phe, Leu, Val, Tyr,
Trp, and

$$-Xaa_{17}-Xaa_{18}-Cys-\backslash Xaa_{20}.$$

~~-Gln-Ala-Cys-Met (SEQ ID NO:102)~~
~~-Leu-Gln-Cys-Trp (SEQ ID NO:103)~~
~~-Met-Ser-Cys-Val (SEQ ID NO:104)~~
~~-Leu-Arg-Cys-Ile (SEQ ID NO:105)~~
~~-Gln-Ala-Cys-Leu (SEQ ID NO:106)~~
~~-Leu-Ser-Cys-Leu (SEQ ID NO:107)~~
~~-Ile-Gly-Cys-Leu (SEQ ID NO:108)~~
~~-Leu-Ala-Cys-Leu (SEQ ID NO:109)~~

-Leu-Ser-Cys-Ile (SEQ ID NO:110)
-Met-Asn-Cys-Leu (SEQ ID NO:111)
-Leu-Arg-Cys-Leu (SEQ ID NO:112)
-Leu-Lys-Cys-Leu (SEQ ID NO:113)
-Leu-Gly-Cys-Leu (SEQ ID NO:114)
-Leu-Asn-Cys-Ile (SEQ ID NO:115)
-Met-Gly-Cys-Leu (SEQ ID NO:116) and
-Met-Ala-Cys-Leu (SEQ ID NO:117).

9. The peptide ligand of claim 6 wherein -Xaa₍₁₇₋₂₀₎ is a four amino acid peptide having the following formula

-Cys-Xaa₁₈-Xaa₁₉-Cys

wherein Xaa₁₈ is an amino acid and Xaa₁₉ is an amino acid.

10. The peptide ligand of claim 9 wherein -Xaa₍₁₇₋₂₀₎ is selected from the group consisting of:

-Cys-Ala-Trp-Cys (SEQ ID NO:118)
-Cys-Ser-Trp-Cys (SEQ ID NO:119)
-Cys-Glu-Pro-Cys (SEQ ID NO:120)
-Cys-Asp-Trp-Cys (SEQ ID NO:121)
-Cys-Glu-Trp-Cys (SEQ ID NO:122)
-Cys-Asn-Trp-Cys (SEQ ID NO:123) and
-Cys-Gly-Trp-Cys (SEQ ID NO:124).

11. The peptide ligand of claim 1 having the formula:

Xaa₍₁₋₁₀₎-Glu-Xaa₁₂-Trp-Xaa₁₄-Cys-Cys-Gly-Pro-Gly-Cys-Xaa₂₁-Xaa₂₂-Xaa₂₃-Xaa₍₂₄₋₂₇₎ (SEQ ID NO:126)

wherein Xaa₍₁₋₁₀₎ is absent or between 1 and 10 amino acids;
Xaa₁₂ is an amino acid;

Xaa₁₄ is an amino acid;

Xaa₂₁ is an amino acid;

Xaa₂₂ is an amino acid;

Xaa₂₃ is an amino acid selected from the group consisting of Val and Leu and

Xaa₍₂₄₋₂₇₎ is absent or between one and four amino acids.

12. The peptide ligand of claim 11 wherein Xaa₍₁₋₁₀₎ is a 10 amino acid peptide having the following formula:

-Cys-Xaa₍₂₋₇₎-Cys-Xaa₉-Gly-; Xaa₍₂₄₋₂₇₎ is a four amino acid peptide having the following formula:

Xaa₍₂₄₋₂₆₎-Cys

wherein Xaa₍₂₋₇₎ is a six amino acid peptide and

Xaa₍₂₄₋₂₆₎ is a 3 amino acid peptide.

13. A peptide ligand having the formula B-B wherein B is the peptide ligand of claim 12 and wherein "-" is an optional linker domain.

14. A peptide ligand having the formula A-B wherein A is the peptide ligand of claim 2 and B is the peptide ligand of claim 11 and wherein "-" is an optional linker domain.

15. The peptide ligand of claim 12 wherein Xaa₍₁₋₁₀₎ has the following formula:

Cys-Xaa₂-Trp-Val-Xaa₅-Xaa₆-Xaa₇-Cys-Xaa₉-Gly- (SEQ ID NO:127).

16. The peptide ligand of claim 15 wherein Xaa₍₁₋₁₀₎ has the following formula:

Cys-Xaa₂-Trp-Val-Xaa₅-Xaa₆-Xaa₇-Cys-Xaa₉-Gly- (SEQ ID NO:127).

and Xaa₂ is an amino acid selected from the group consisting of Ala and Ser;

Xaa₅ is an amino acid selected from the group consisting of Ser, Leu, Ala, Arg and Val;

Xaa₆ is an amino acid selected from the group consisting of Phe, Val and Leu;

Xaa₇ is an amino acid selected from the group consisting of Asp, Gln, Tyr, Trp, Leu and His and

Xaa₉ is an amino acid selected from the group consisting of Gly, Phe and Leu.

17. The peptide ligand of claim 16 wherein Xaa₍₁₋₁₀₎ has the following formula:

Cys-Ser-Trp-Val-Leu-Xaa₆-Xaa₇-Cys-Gly-Gly- (SEQ ID NO:162).

18. The peptide ligand of claim 17 wherein Xaa₍₂₄₋₂₆₎ has the following formula:

Xaa₂₄-Xaa₂₅-Xaa₂₆ and

Xaa₂₄ is an amino acid selected from the group consisting of Trp, Val, Gly and Ala;

Xaa₂₅ is an amino acid selected from the group consisting of Asn, Lys, Asp, Glu and His and

Xaa₂₆ is an amino acid selected from the group consisting of Ala, Ser and Val.

19. The peptide ligand of claim 17 wherein Xaa₍₂₄₋₂₆₎ has the following formula:

Xaa₂₄-Xaa₂₅-Xaa₂₆ and

Xaa₂₄ is an amino acid selected from the group consisting of Trp, Val, Gly and Ala;

Xaa₂₅ is an amino acid selected from the group consisting of Asn, Lys, Asp, Glu and His and

Xaa₂₆ is an amino acid selected from the group consisting of Ala, Ser and Val.

20. The peptide ligand of claim 19 wherein

Xaa₂₄ is Val;

Xaa₂₅ is Asn and

Xaa₂₆ is Ala.

21. A polypeptide which comprises:

(a) a peptide ligand according to any of claims 1, 4, 11, or 13 and

(b) an immunoglobulin constant region sequence.

22. The polypeptide of claim 21 further comprising a linker sequence.

23. The polypeptide of claim 20 or 21 wherein the immunoglobulin constant region sequence is the constant domain of an IgG heavy chain.

24. The polypeptide of claim 22 wherein said constant region sequence comprises the CH3 domain of an immunoglobulin heavy chain.

25. The polypeptide of claim 24 further comprising the hinge region of an immunoglobulin heavy chain.

27. The polypeptide of claim 21 further comprising an additional functional moiety.

29. The polypeptide of claim 27 wherein the additional functional moiety is a cytotoxic agent.

31. A pharmaceutical composition comprising the polypeptide of claim 21 and a pharmaceutically acceptable excipient.

32. A pharmaceutical composition comprising the polypeptide of claim 28 and a pharmaceutically acceptable excipient.

33. An isolated DNA molecule encoding the peptide ligand of claim 1.

34. The DNA molecule of claim 33 further comprising an expression control sequence operably linked to the DNA molecule.

35. An expression vector comprising the DNA molecule of claim 33 wherein the control sequence is recognized by a host cell transformed with the vector.

36. A host cell transformed with the vector of claim 35.

37. A method for expressing a DNA molecule encoding a peptide ligand in a host cell, comprising culturing the host cell of claim 36 under conditions suitable for expression of the peptide ligand.

38. The method of claim 37 further comprising recovering the peptide ligand from the culture medium.

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